PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
A61K 9/14, 9/48, B01J 13/02

A1

(11) International Publication Number: **WO 95/09613**

(43) International Publication Date: 13 April 1995 (13.04.95)

(21) International Application Number: PCT/US93/10611

(22) International Filing Date: 4 November 1993 (04.11.93)

(30) Priority Data:
08/131,287 4 October 1993 (04.10.93) US

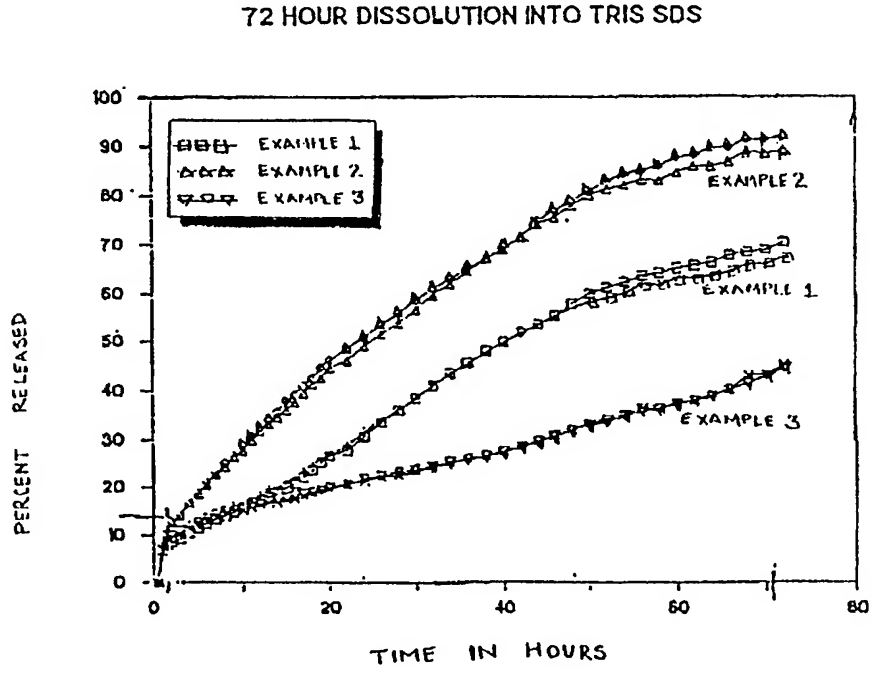
(71)(72) Applicants and Inventors: CHASIN, Mark [US/US]; 3 Wayne Court, Manalapan, NJ 07726 (US). TIGNER, Joseph [US/US]; 1 Santa Lane, New Milford, CT 06776 (US). HOTZ, Joyce, M. [US/US]; 6655 Fernshire Court, Mason, OH 45050 (US). ATKINS, Thomas [US/US]; 11708 Jauk Valley Lane, Cincinnati, OH 45249 (US).

(74) Agents: DAVIDSON, Clifford, M. et al.; Steinberg and Raskin, 1140 Avenue of the Americas, New York, NY 10036 (US).

(81) Designated States: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: CONTROLLED RELEASE MICROSPHERES



(57) Abstract

An injectable preparation is disclosed in which a therapeutically effective drug such as a local anesthetic is dispersed in microspheres of a biodegradable controlled release polymeric material, such as a polyanhydride or a polyorthoester. In certain embodiments, the polymeric material is composed of a copolymer of lactic acid and/or glycolic acid. The injectable preparation is capable of providing prolonged anesthesia to a desired area of treatment in an animal or human.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**GB**	United Kingdom	**MR**	Mauritania
AU	Australia	**GE**	Georgia	**MW**	Malawi
BB	Barbados	**GN**	Guinea	**NE**	Niger
BE	Belgium	**GR**	Greece	**NL**	Netherlands
BF	Burkina Faso	**HU**	Hungary	**NO**	Norway
BG	Bulgaria	**IE**	Ireland	**NZ**	New Zealand
BJ	Benin	**IT**	Italy	**PL**	Poland
BR	Brazil	**JP**	Japan	**PT**	Portugal
BY	Belarus	**KE**	Kenya	**RO**	Romania
CA	Canada	**KG**	Kyrgystan	**RU**	Russian Federation
CF	Central African Republic	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CG	Congo			**SE**	Sweden
CH	Switzerland	**KR**	Republic of Korea	**SI**	Slovenia
CI	Côte d'Ivoire	**KZ**	Kazakhstan	**SK**	Slovakia
CM	Cameroon	**LI**	Liechtenstein	**SN**	Senegal
CN	China	**LK**	Sri Lanka	**TD**	Chad
CS	Czechoslovakia	**LU**	Luxembourg	**TG**	Togo
CZ	Czech Republic	**LV**	Latvia	**TJ**	Tajikistan
DE	Germany	**MC**	Monaco	**TT**	Trinidad and Tobago
DK	Denmark	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**US**	United States of America
FI	Finland	**ML**	Mali	**UZ**	Uzbekistan
FR	France	**MN**	Mongolia	**VN**	Viet Nam
GA	Gabon				

CONTROLLED RELEASE MICROSPHERES

BACKGROUND OF THE INVENTION

The present invention is related to biodegradable controlled release formulations for the administration of locally active drugs, in particular, local anesthetics.

While compounds utilized as general anesthetics reduce pain by producing a loss of consciousness, local anesthetics act via a loss of sensation in the localized area of administration in the body. The mechanism by which local anesthetics induce their effect, while not having been determined definitively, is generally thought to be based upon the ability to interfere with the initiation and transmission of the nerve impulse. The duration of action of a local anesthetics is proportional to the time during which it is in actual contact with the nervous tissues. Consequently, procedures or formulations that maintain localization of the drug at the nerve greatly prolong anesthesia.

All local anesthetics are toxic, and therefore it is of great importance that the choice of drug, concentration, rate and site of administration, as well as other factors, be considered in their use. On the other hand, a local anesthetic must remain at the site long enough to allow sufficient time for the localized pain to subside.

Different devices and formulations are known in the art for administration of local anesthetics. For example, U.S. Patent Nos. 4,725,442 and 4,622,219 (Haynes) are directed to microdroplets of methoxyflurane-containing

microdroplets coated with a phospholipid prepared by sonication, which are suitable for intradermal or intravenous injection into a patient for inducing local anesthesia. Such microdroplets are said to cause long-term local anesthesia when injected intradermally, giving a duration of anesthesia considerably longer than the longest acting conventional local anesthetic (bupivacaine).

U.S. Patent No. 5,188,837 (Domb) relates to a microsuspension system containing liposphereres having a layer of a phospholipid imbedded on their surface. The core of the liposphere is a solid substance to be delivered, or the substance to be delivered is dispersed in an inert vehicle. The substance to be delivered can be, e.g., nonsteroidal anti-inflammatory compounds, local anesthetics, water insoluble chemotherapeutic agents and steroids.

Other formulations directed to injectable microcapsules, etc. are known. For example, U.S. Patent No. 5,061,492 related to prolonged release microcapsules of a water-soluble drug in a biodegradable polymer matrix which is composed of a copolymer of glycolic acid and a lactic acid. The microcapsules are prepared as an injectable preparation in a pharmaceutically acceptable vehicle. The particles of water soluble drug is retained in a drug-retaining substance dispersed in a matrix of the lactic/glycolic acid copolymer in a ratio of 100/0 to 50/50 and an average molecular weight of 5,000-200,000. The injectable preparation is made by preparing a water-in-oil emulsion of aqueous layer of drug and drug retaining substance and an oil layer of the polymer, thickening and then water-drying.

U.S. Patent No. 4,938,763 (Dunn, et al.) is related to a biodegradable polymer for use in providing syringeable, in-situ forming, solid biodegradable implants for animals. In one aspect of this reference, a thermosetting system is utilized which utilizes copolymers which may be derived

from polylactides and/or polyglycolides, combinations and mixtures of these and other polymers.

U.S. Patent No. 4,293,539 (Ludwig, et al.) is directed to controlled release formulations comprised of a microbial agent dispersed throughout a copolymer derived from lactic acid and glycolic acid. The copolymer is derived from 60-95% lactic acid and 40-5% glycolic acid by weight, and has a molecular weight of 6,000-35,000. An effective amount of the copolymeric formulation is administered by subcutaneous or intramuscular administration.

OBJECTS AND SUMMARY OF THE INVENTION

It is an object of the present invention to provide a biodegradable controlled release dosage form for prolonged treatment of localized areas in humans and animals.

It is a further object of the present invention to provide a method for prolonging the effect of a local anesthetic agent at a desired site of treatment which is safe, effective, and which effectively controls post-operative pain.

These objects and others are accomplished by the present invention, which is directed to a biodegradable controlled release formulation capable of delivering an effective dose of a local anesthetic over a prolonged period of time, comprising microspheres of from about 5 to about 95 percent of a local anesthetic, and from about 5 to about 95 percent of a polymeric material selected from the group consisting of a polylactide, a polyglycolide, a poly(lactide-co-glycolide), a polyanhydride, a polyorthoester and mixtures of any of the foregoing. In one preferred embodiment, the polymeric material is derived from about 0 to about 100 percent lactic acid and from about 100 to about 0 percent glycolic acid, by weight.

The microspheres of the biodegradable controlled release formulation are preferably dispersed in a pharmaceu-

tically acceptable medium for injection into humans or animals.

The biodegradable controlled release formulations of the present invention provide a desired prolonged release of drug at the site of treatment, and may provide the desired effect, e.g., for 1-3 days or longer, even as long as months.

The present invention also relates to a method of providing prolonged anesthesia in a localized area in an animal or human, comprising injecting into a localized area to be treated an effective amount of controlled release biodegradable microspheres comprising from about 5 to about 95 percent of a local anesthetic and from about 5 to about 95 percent by weight of a polymeric material selected from the group consisting of a polylactide, a polyglycolide, a poly(lactide-co-glycolide), a polyanhydride, a polyorthoester, a polyanhydride, a polyorthoester, and mixtures of any of the foregoing.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings are illustrative of embodiments of the invention and are not meant to limit the scope of the invention as encompassed by the claims.

Fig. 1 is a graphical representation of the dissolution data obtained for Examples 1-3;

Fig. 2 is a graphical representation comparing the dissolution data obtained for Example 6 (spray-drying process) and Example 9 (solvent extraction process); and

Fig. 3 is a graphical representation of the dissolution data obtained for Examples 4-5 (spray-drying process) and Examples 7-8 (solvent extraction process).

DETAILED DESCRIPTION

The controlled release microspheres of the present invention are comprised of the therapeutically active agent

(i.e., drug), and a polymeric material selected from the group consisting of a polylactide, a polyglycolide, a poly(lactide-co-glycolide), a polyanhydride, a polyorthoester and mixtures of any of the foregoing. In certain embodiments, the microspheres include from about 5% to about 95% drug and from about 5% to about 95% polymer, by weight. In certain preferred embodiments, the drug is included in the microspheres in an amount from about 20% to about 75%, and more preferably from about 25%-40% (low-load microspheres) and from about 40% to about 75% (high-load microspheres).

The term "microspheres" are defined for purposes of the present invention as particles comprising local anesthetic and the aforementioned polymeric materials (used as a controlled release carrier for the drug) which are preferably anywhere from about 20 microns to about 200 microns, and more preferably from about 45 to about 90 microns in diameter. The microspheres are preferably formed in such a size as to be injectable. For purposes of the present invention, the term "microsphere" encompasses "microparticle" and "microcapsule". The polymeric material used in the microspheres of the present invention preferably have a molecular weight from about 5,000 to about 200,000.

Other biodegradable polymers which may be useful in the present invention are block copolymers of polyethylene oxide and lactide/glycolide, polyglutamic acid polymers, polycaprolactones, polydioxanones, polyketals, polycarbonates, polyorthocarbonates, polyamides, polyesteramides, polyurethanes, polyphosphazenes, polyhydroxybutyrates, polyhydroxyvalerates, polyalkylene oxalates and succinates, poly(malic acid), poly(amino acids), polyvinylpyrollidone, chitan, chitosan, and mixtures of any of the foregoing.

Preferably, the polymeric material used in the present invention is a polylactic acid polymer, a polyglycolic acid

polymer, or a copolymer derived from a combination of lactic acid and glycolic acid.

The polymeric material may be prepared by any method known to those skilled in the art. For example, where the polymeric material is comprised of a copolymer of lactic and glycolic acid, this copolymer may be prepared by the procedure set forth in U.S. Patent No. 4,293,539 (Ludwig, et al.), hereby incorporated by reference. Basically, therein the copolymers are prepared by condensation of lactic acid and glycolic acid in the presence of a readily removable polymerization catalyst (e.g., a strong acid ion-exchange resin such as Dowex HCR-W2-H). The amount of catalyst is not critical to the polymerization, but typically is form about 0.01 to about 20 parts by weight relative to the total weight of combined lactic acid and glycolic acid. The polymerization reaction may be conducted without solvents at a temperature from about 100° C to about 250° C for about 48 to about 96 hours, preferably under a reduced pressure to facilitate removal of water and by-products. The copolymer is then recovered by filtering the molten reaction mixture to remove substantially all of the catalyst, or by cooling and then dissolving the reaction mixture in an organic solvent such as dichloromethane or acetone and then filtering to remove the catalyst.

Polyanhydrides may be prepared in accordance with the methods set forth in U.S. Patent No. 4,757,128, hereby incorporated by reference. For example, polyanhydrides may be synthesized by melt polycondensation of highly pure dicarboxylic acid monomers converted to the mixed anhydride by reflux in acetic anhydride, isolation and purification of the isolated prepolymers by recrystallization, and melt polymerization under low pressure (10^{-4} mm) with a dry ice/acetone trap at a temperature between 140°-250° C. for 10-300 minutes. High molecular weight polyanhydrides are obtained by inclusion of a catalyst which increases the

rate of anhydride interchain exchange, for example, alkaline earth metal oxides such as CaO, BaO and $CaCO_3$. Polyorthoester polymers may be prepared, e.g., as set forth in U.S. Patent No. 4,070,347, hereby incorporated by reference.

Various commercially available poly (lactide-co-glycolide) materials (PLGA) may be used in the preparation of the microspheres of the present invention. For example, poly(d,l-lactic-co-glycolic acid) are commercially available from Medisorb Technologies International L.P. (Cincinnati, OH). A preferred product commercially available from Medisorb is a 50:50 poly (D,L) lactic co-glycolic acid known as MEDISORB 5050 DL. This product has a mole percent composition of 50% lactide and 50% glycolide. Other suitable commercially available products are Medisorb 65:35 DL, 75:25 DL, 85:15 DL and poly(d,l-lactic acid) (d,l-PLA). Poly(lactide-co-glycolides) are also commercially available from Boerhinger Ingelheim (Germany) under its Resomer© mark, e.g., PLGA 50:50 (Resomer RG 502), PLGA 75:25 (Resomer RG 752) and d,l-PLA (resomer RG 206), and from Birmingham Polymers (Birmingham, Alabama). These copolymers are available in a wide range of molecular weights and ratios of lactic to glycolic acid.

Pharmaceutically acceptable polyanhydrides which are useful in the present invention have a water-labile anhydride linkage. The rate of drug release can be controlled by the particular polyanhydride polymer utilized and its molecular weight. The polyanhydride polymer may be branched or linear. Examples of polyanhydrides which are useful in the present invention include homopolymers and copolymers of poly(lactic acid) and/or poly(glycolic acid), poly[bis(p-carboxyphenoxy)propane anhydride] (PCPP), poly[bis(p-carboxy)methane anhydride] (PCPM), polyanhydrides of oligomerized unsaturated aliphatic acids, polyanhydride polymers prepared from amino acids which are

modified to include an additional carboxylic acid, aromatic polyanhydride compositions, and co-polymers of polyanhydrides with other substances, such as fatty acid terminated polyanhydrides, e.g., polyanhydrides polymerized from monomers of dimers and/or trimers of unsaturated fatty acids or unsaturated aliphatic acids.

The biodegradable controlled release microspheres of the present invention may be prepared by any procedure known to those skilled in the art. In certain preferred embodiments, however, the microspheres may be obtained by utilizing a solvent extraction technique (reactor process) which involves dissolving the drug and the polymer in an organic solvent such as ethyl acetate. This solution thereby obtained (the dispersed phase) is added to a solution of, e.g., polyvinyl alcohol (PVA) in water (the continuous phase) with stirring. The emulsion thereby formed is then added to water in order to extract the solvent and to harden the microspheres. The mixture is then filtered and the microspheres are dried. One appropriate method of drying is, e.g., under vacuum at room temperature. The desired particle size fraction is then collected by sieving. The organic solvent utilized is preferably ethyl acetate; however, any pharmaceutically acceptable organic solvent may be utilized, such as acetone, ethanol, diethyl ether, methanol, benzyl alcohol, methylene chloride, petroleum ether or others. This procedure is particularly useful for preparing microspheres of bupivacaine base.

Alternatively, the microspheres of bupivacaine base may be prepared by dissolving the drug and polymer in ethyl acetate and thereafter spray drying the solution.

In instances where the microspheres are to incorporate drugs which are very water soluble and insoluble in ethyl acetate, such as bupivacaine HCl, the microspheres may be prepared using a coacervation/ phase separation rather than the solvent extraction technique described above. However,

the solvent extraction technique can be used with bupivacaine HCl due to its low water solubility at pH 7.4 and above. The coacervation/phase separation technique utilized involves dissolving the polymer in ethyl acetate and suspending micronized bupivacaine HCl in the solution. Silicone oil is then added to form the microspheres. This mixture is then added to heptane to harden the microspheres, which are then separated by filtration. The microspheres are dried under a vacuum at room temperature. The desired particle size fraction is then collected by sieving.

Alternatively, microspheres prepared using bupivacaine HCl may be accomplished by suspending the drug in a solution of polymer in ethyl acetate or in methylene chloride and methanol and spray drying.

Alternatively, the bupivacaine HCl may be dissolved in water, and the polymer may be dissolved in ethyl acetate. The water phase then can be added to the organic phase and homogenized to yield a W/O emulsion. The drug being in the water phase would then be surrounded by polymer (oil phase). This is then added to the PVA solution in water with stirring to form a W/O/W emulsion. The solvent would diffuse out, leaving microspheres. Additional cold water can be added to harden the microspheres. This process may yield more uniform microspheres without requiring micronization of the drug. Also, as the drug will be surrounded by polymer, the release of the drug may be more uniform and would be diffusion-controlled.

The ultimate drug content of the microspheres according to the present invention may be varied substantially, depending upon whether a high load or a low load formulation procedure is utilized. In certain preferred embodiments (e.g., where the drug is bupivacaine), the drug content of the high-load microspheres may be from about 40% to about 95% of the total weight of the microsphere, and

the drug content of the low-load microspheres may be from about 5% to about 40%.

The drug included in the microspheres may be one which would be useful in a localized setting, such as a local anesthetic, anti-inflammatory, antifungal agents, antiviral agents, anti-parasitic agents or antibiotic. However, virtually any bioactive compound can be utilized in the microspheres of the present invention, including, but not limited to, vitamins, nucleic acids, polynucleotides, polysaccharides, immunomodulators, dyes, radiolabels, radioopaque compounds, fluorescent compounds, hormones, neurotransmitters, glycoproteins, lipoproteins, immumoglobulins, peptides, proteins, enzymes, and the like.

In one preferred embodiment of the present invention, the drug included in the microspheres is a local anesthetic either of the ester or amide type. Suitable local anesthetics of the ester type include the benzoic acid esters (e.g., piperocaine, meprylcaine, isobucaine), the paraaminobenzoic acid esters (e.g., procaine, tetracaine, butethamine, propoxycaine, chloroprocaine); meta-aminobenzoic acid esters (e.g., metabutethamine, primacaine), paraethoxybenzoic acid esters (e.g., parethoxycaine), and their pharmaceutically acceptable salts. The non-esters include, e.g., lidocaine, mepivacaine, pyrrocaine, prilocaine, bupivacaine, etidocaine, pharmaceutically acceptable salts. A most preferred local anesthetic is bupivacaine.

In certain preferred embodiments of the present invention, the microspheres incorporate bupivacaine as the drug in an amount from about 45% to about 70% by weight, the copolymer being PLGA 50:50 of a molecular weight from about 5,000 to about 200,000.

The microspheres of the present invention preferably provide a sustained action in the localized area to be treated. For example, when the drug included in the microspheres is bupivacaine, it would be desirable that such a

formulation could provide localized anesthesia to the area in question for a period of one day, two days, three days, or longer. The formulations can therefore, of course, be modified in order to obtain such a desired result.

The microspheres of the present invention may be utilized as a controlled release formulation preferably by incorporating an effective amount of the same into a pharmaceutically acceptable solution (e.g., water) or suspension for injection. The final reconstituted product viscosity may be in a range suitable for the route of administration. In certain instances, the final reconstituted product viscosity may be, e.g., about 35 cps. Administration may be via the subcutaneous or intramuscular route. However, alternative routes are also contemplated, and the formulations may be applied to the localized site in any manner known to those skilled in the art, such that a localized effect is obtained. The microspheric formulations of the present invention can be implanted at the site to be treated. Thereby, the formulations of the present invention, when including a local anesthetic, may be used in the control of post-operative pain.

The dosage of the controlled release microsphere formulations of the present invention is dependent upon the kind and amount of the drug to be administered, the recipient animal, and the objectives of the treatment. For example, when the drug included in the microspheres of the present invention is bupivacaine, the formulation may include, e.g., from about 0.7 to about 2 mg/kg body weight. For a 70 kg human or animal, this would be from about 50 to about 150 mg. Since the formulations of the present invention are controlled release, it is contemplated that formulations may include as much as 120 mg/kg bupivacaine or more.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following examples illustrate various aspects of the present invention. They are not to be construed to limit the claims in any manner whatsoever.

EXAMPLES 1-3 (SOLVENT EXTRACTION PROCESS)

In Examples 1-3, bupivacaine microspheres are prepared by dissolving the bupivacaine base and the polymer in ethyl acetate. The polymer is 50:50 poly (D,L) lactic co-glycolic acid which has a mole percent composition of 50% lactide and 50% glycolide (commercially available from Medisorb under the tradename Medisorb 5050 DL). This dispersed phase is then added to a solution of polyvinyl alcohol (PVA) in water (the continuous phase) with stirring. The resulting emulsion is monitored for droplet size, which is in turn controlled by the rate of stirring. The emulsion is then added to water to extract the solvent and to harden the microspheres. The mixture is then filtered and the microspheres are dried under vacuum at room temperature. The desired particle size fraction is then collected by sieving.

Each of Examples 1-3 are prepared such that the microspheres have a relatively high drug content. In Example 1, the theoretical drug content is about 60%, and the size of the microspheres range from about 45 to about 90 microns. In Example 2, the theoretical drug content is about 61%, and the range in the size of the microspheres is from about 45 to about 63 microns. In Example 3, the theoretical drug content is about 65%, and the range in particle size of the microspheres is from about 45 to about 63 microns.

The microspheres of Examples 1-3 are then suspended in a suitable media for injection, in this case water. Thereafter, the microspheres are subjected to in-vitro dissolution testing. An automated dissolution test method is

utilized using the USP/NF Paddle Method II. The dissolution medium is 900 ml of Tris buffer with 0.05% sodium dodecyl sulfate at pH 7.4 at 37° C with a stirring speed of about 50 RPM. The surfactant is added in order to prevent the microspheres from floating on the surface of the dissolution medium. The dissolution data for the microspheres of Examples 1-3 are presented in Fig. 1, and further information concerning these formulations is presented in Table 1 below.

TABLE 1

Formulation	Microsphere Size Range	Theoretical % Drug	Actual % Drug	50:50 dl-PLGA Polymer-MW	In-vitro Release 24 hrs	72 hrs
Ex. 1	45-90μ	62%	47%	--	28%	68%
Ex. 2	45-63μ	61%	56%	50K	52%	91%
Ex. 3	45-63μ	65%	59%	50K	22%	46%

From the results set forth in Fig. 1 and Table 1, no correlation between drug content and release rate can be readily made.

It was expected that the formulation of Example 3 would release drug faster than that of Example 1 because of a higher drug content. However, the in-vitro release for Example 3 was slower than expected. It is hypothesized that this is due to the glass transition temperature of the polymer being lowered (below about 37°C) by the high drug content. This situation may or may not be translated into in-vivo results.

EXAMPLES 4-9 (SPRAY-DRIED)

In Examples 4-9, the bupivacaine base and the polymer utilized in Examples 1-3 are once again dissolved in ethyl acetate, but this time the microspheres are obtained by spray-drying the solution. Example 4 utilizes a relatively

high drug content, whereas Example 5 utilizes a relatively low drug content. In Examples 7-9, microspheres having a substantially similar drug content to Examples 4-5 are prepared using the solvent extraction technique utilized in Examples 1-3. Details of the formulations are presented in Table 2 below.

TABLE 2

Formulation	Drug Content (Theoretical)	Yield	Process
Ex. 4	49%	55%	Spray-Dried
Ex. 5	29%	64%	Spray-Dried
Ex. 6	45%	--	Spray-Dried
Ex. 7	47%	62%	Solvent Extraction
Ex. 8	28%	74%	Solvent Extraction
Ex. 9	60%	60%	Solvent Extraction

With regard to Example 9, the actual percentage of bupivacaine base in the microspheres is 51%, the molecular weight of the 50:50 dl-PLGA polymer is 18,000, the microspheres were about 45-63 microns, and in-vitro dissolution conducted as in Examples 1-3 showed that 61% of the bupivacaine was released in 22 hours.

The microspheres of Examples 6 and 9 are suspended in a suitable injection medium (e.g., water) and then subjected to in-vitro dissolution testing via the procedures set forth in Examples 1-3. The in-vitro dissolution results are determined for 22 hours, and are graphically depicted in Fig. 2.

In Fig. 3, the in-vitro dissolutions of Examples 4-5 and 7-8 are determined as per the Examples above, and compared to the dissolution of the bupivacaine free base and the bupivacaine hydrochloride salt forms. As can be seen from the graph of Fig. 3, when compared to pure bupivacaine base, each of Examples 4-5 and 7-8 showed a distinct retarding effect in their dissolution profile.

Furthermore, all four examples of the invention displayed a small initial burst of drug release which was more pronounced in the microspheres prepared by the spray-dried process as compared to the examples prepared by the solvent extraction process.

Scanning electron micrographs of the microspheres for the formulations prepared by the solvent extraction and by the spray-dried technique are then compared. The spray-dried process yields microspheres which are smaller than with the solvent extraction process.

The examples provided above are not meant to be exclusive. Many other variations of the present invention would be obvious to those skilled in the art, and are contemplated to be within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. A biodegradable controlled release formulation capable of delivering an effective dose of a local anesthetic over a prolonged period of time, comprising microspheres of

a local anesthetic and a controlled release polymeric material selected from the group consisting of a polylactide, a polyglycolide, a copolymer derived from lactic acid and glycolic acid, a polyanhydride, a poly-orthoester, and mixtures of any of the foregoing.

2. The biodegradable controlled release microspheres of claim 1, wherein said polymeric material is derived from about 5 to about 95 percent lactic acid and from about 95 to about 5 percent glycolic acid, by weight.

3. The biodegradable controlled release microspheres of claims 1-2, wherein said local anesthetic is bupivacaine.

4. The biodegradable controlled release microspheres of claim 1, wherein said polymeric material provides a controlled release of said local anesthetic for at least about 24 hours.

5. The biodegradable controlled release microspheres of claim 2, wherein said polymeric material is a 50:50 poly (D,L) lactic co-glycolic acid copolymer.

6. The biodegradable controlled release microspheres of claim 3, wherein said microspheres comprise from about 40 to about 70 percent bupivacaine, by weight.

7. The biodegradable controlled release microspheres of claim 3, wherein said microspheres comprise from about 25 to about 40 percent bupivacaine, by weight.

8. The biodegradable controlled release microspheres of claims 1-7, wherein said microspheres are dispersed or suspended in a pharmaceutically acceptable medium for injection into humans or animals.

9. The biodegradable controlled release microspheres of claim 1, which provide a controlled release of said local anesthetic for at least about 3 days.

10. The biodegradable controlled release microspheres of claims 1, 2, 3 and 9, wherein the local anesthetic is selected from the group consisting of benzoic acid esters, para-aminobenzoic acid esters, meta-aminobenzoic acid esters, para-ethoxybenzoic acid esters, lidocaine, mepivacaine, pyrrocaine, prilocaine, bupivacaine, etidocaine, and mixtures of any of the foregoing.

11. A method of providing prolonged anesthesia in a localized area in a human or animal, comprising

injecting into a localized area to be anesthetized an effective amount of controlled release biodegradable microspheres comprising from about 5 to about 95 percent of a local anesthetic and from about 5 to about 95 percent by weight of a polymeric material consisting of a polylactide, a polyglycolide, a copolymer derived from lactic acid and glycolic acid, a polyanhydride, a polyorthoester, and mixtures of any of the foregoing.

12. The method of claim 11, wherein said polymeric material consists of from about 5 to about 95 percent lactic acid and from about 95 to about 5 percent glycolic acid, by weight.

13. The method of claim 11, further comprising preparing said microspheres such that said local anesthetic is released from said polymeric material such that the localized area is anesthetized for at least about 24 hours.

14. The method of claims 11-13, wherein said local anesthetic is selected from the group consisting of benzoic acid esters, para-aminobenzoic acid esters, meta-aminobenzoic acid esters, para-ethoxybenzoic acid esters, lidocaine, mepivacaine, pyrrocaine, prilocaine, bupivacaine, etidocaine, and mixtures of any of the foregoing.

15. The method of claim 11, wherein said local anesthetic is bupivacaine.

16. The method of claim 15, further comprising injecting a suitable number of microspheres to provide a dose from about 0.7 mg/kg to about 120 mg/kg bupivacaine, based on the body weight of the human or animal to be treated.

17. The method of claim 11, further comprising preparing said microspheres by dissolving bupivacaine base and said polymeric material in a suitable solvent, and then spray-drying the resultant solution to obtain said microspheres.

18. The method of claim 11, further comprising preparing said microspheres by dissolving said local anesthetic and said polymer in an organic solvent, adding the resultant solution to a solution of polyvinyl alcohol in water, and thereafter extracting said solvent and hardening said microspheres.

19. An injectable preparation comprising a local anesthetic dispersed in microspheres of a biodegradable controlled release polymer, polylactide, a polyglycolide, a copolymer derived from lactic acid and glycolic acid, a polyanhydride, a polyorthoester, and mixtures of any of the foregoing said polymer having an average molecular weight from about 5,000 to about 200,000, said microspheres having an average diameter from about 20 microns to about 200 microns, said microspheres being dispersed in a pharmaceutically acceptable vehicle for injection, said preparation capable of providing anesthesia to a desired localized area in a human or animal for at least about 24 hours.

20. The injectable preparation of claim 19, wherein said copolymer is a 50:50 poly (D,L) lactic co-glycolic acid copolymer.

21. The injectable preparation of claim 19, which provides anesthesia to a localized region when administered for at least about three days.

22. The injectable preparation of claims 19-21, wherein said local anesthetic is selected from the group consisting of benzoic acid esters, para-aminobenzoic acid esters, meta-aminobenzoic acid esters, para-ethoxybenzoic acid esters, lidocaine, mepivacaine, pyrrocaine, prilocaine, bupivacaine, etidocaine, and mixtures of any of the foregoing.

23. The injectable preparation of claim 22, which comprises a suitable number of microspheres to provide a dose from about 0.7 mg/kg to about 120 mg/kg bupivacaine, based on the body weight of the human or animal to be treated.

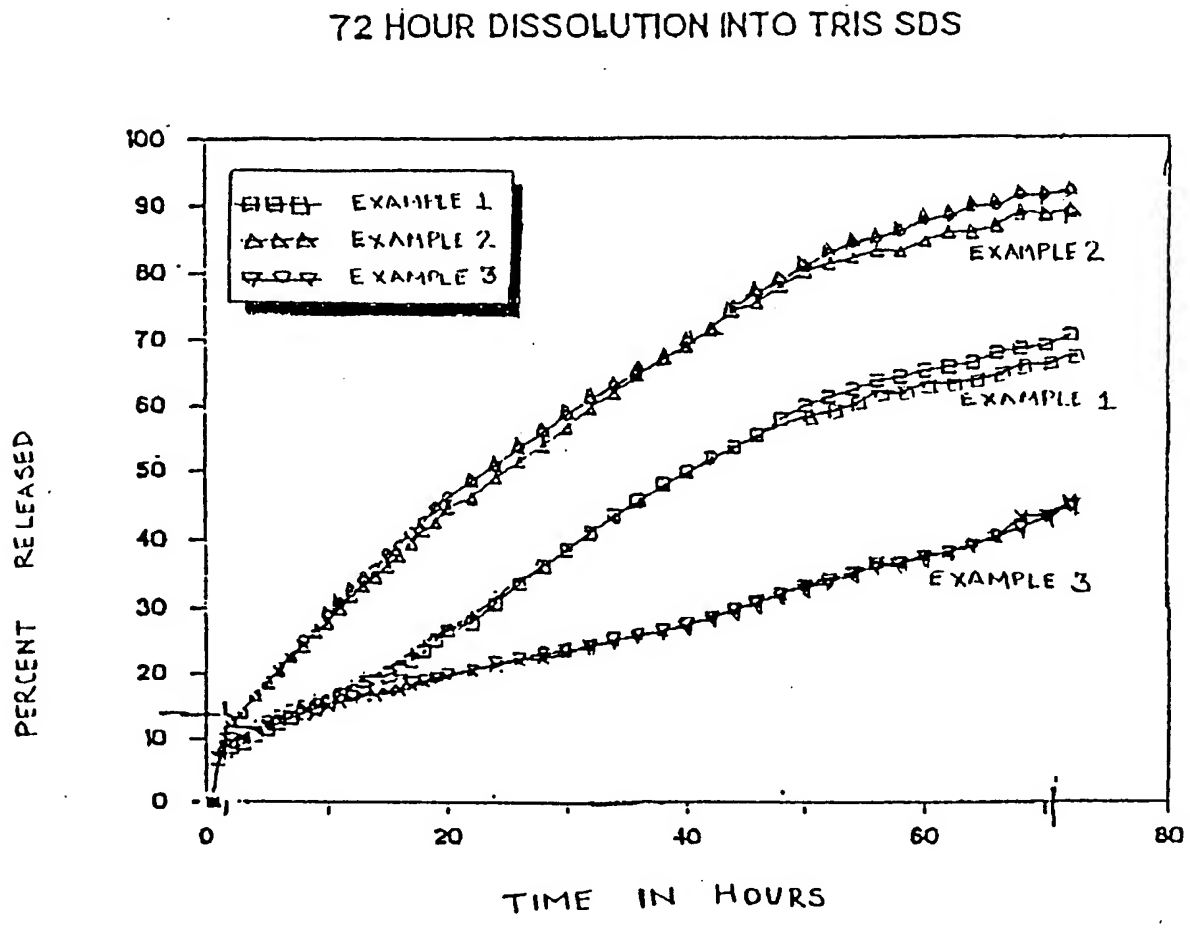

72 HOUR DISSOLUTION INTO TRIS SDS
EXAMPLE 1
EXAMPLE 2
EXAMPLE 3
PERCENT RELEASED
TIME IN HOURS
0
10
20
30
40
50
60
70
80
90
100
0
20
40
60
80

Fig. 1

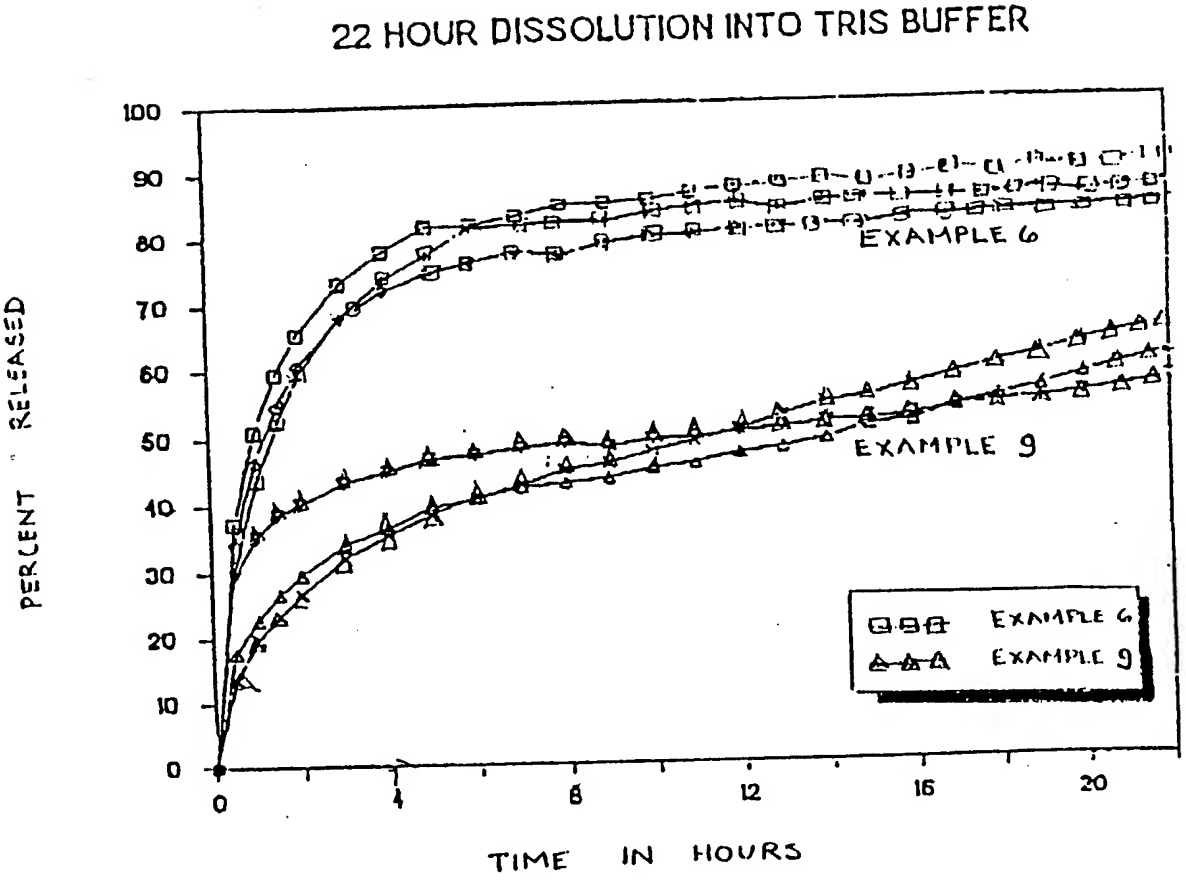

22 HOUR DISSOLUTION INTO TRIS BUFFER
PERCENT RELEASED
100
90
80
70
60
50
40
30
20
10
0
0
4
8
12
16
20
TIME IN HOURS
EXAMPLE 6
EXAMPLE 9
EXAMPLE 6
EXAMPLE 9

Fig. 2

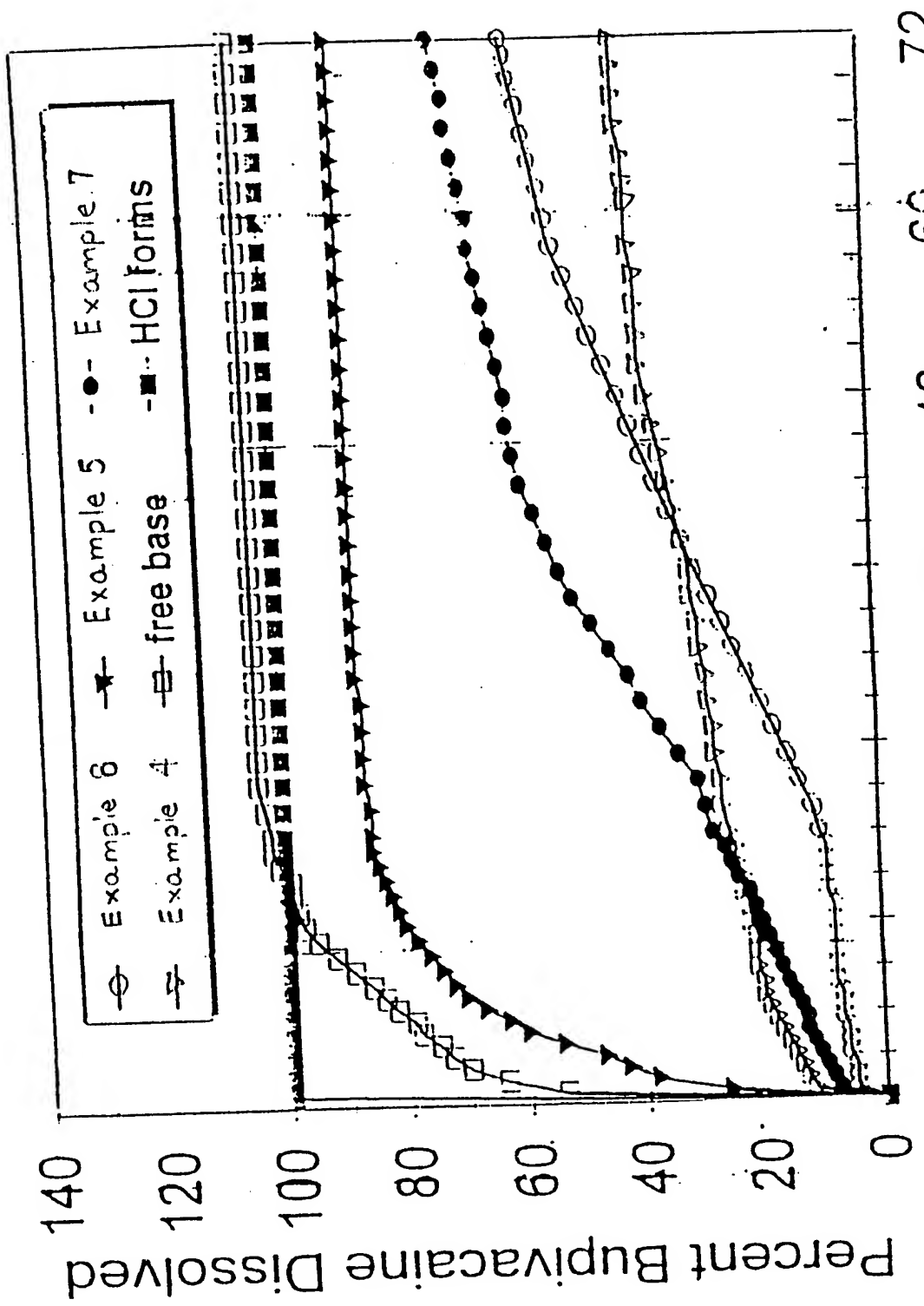

Percent Bupivacaine Dissolved
140
120
100
80
60
40
20
0
0
12
24
36
48
60
72
Time, Hours
Example 8
Example 5
Example 7
Example 4
free base
HCl forms

Fig. 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/10611

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 9/14, 9/48; B01J 13/02
US CL :424/451, 489; 514/963; 264/4.1, 4.33, 4.6
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/451, 489; 514/963; 264/4.1, 4.33, 4.6

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 4,623,588 (NUWAYSER ET AL) 18 November 1986, column 2, line 52 and 60-65; column 4, lines 28-35, 39-40.	1, 2, 4,5, 9, 11-13, 15, 19-21
Y		16
Y	US, A, 4,384,975 (FONG) 24 MAY 1983, column 1, line 42, 35-57; column 5, 14-17, 63-67.	17-18

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
14 MARCH 1994

Date of mailing of the international search report
APR 06 1994

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703) 305-3230

Authorized officer
CARLOS AZPURU
Telephone No. (703) 308-2351

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/10611

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,384,975 (FONG) 24 MAY 1983, column 1, line 42, 35-57; column 5, 14-17, 63-67.17-18	